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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/202,984	Czernilofsky
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Apr 17, 2003*.

2a) [X] This action is **FINAL.** 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *28-60* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *28-53 and 55-60* is/are rejected.

7) [X] Claim(s) *54* is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [X] Other: *Detailed Action*

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 28-44, 46, 49-51, 53, 55-56, and 58-60 are rejected under 35 U.S.C. 103 (a) over Foulkes et al. (PCT international Publication number WO 92/13063) (August 6, 1992) in view of Fodor et al. (U.S. Patent 6,309,822 B1) (October 30, 2001).

Foulkes et al teach a process for determining the pharmacological effect of a substance on the activity of various biological target molecules, wherein a substance is applied to test cells which contain one or more biological target molecules and the effect of the substance on the

activity of the target molecules is determined, characterized in that test cells are derived or not derived from one type of tissues and one species (Claims 67-72 and 104 and Page 56, line 5 to page 61, line 20) and

a) a defined amount of a test substance is applied to test cells which differ in that they contain one or more different biological target molecules (Claims 67-72 and Claims 92-102 and page 56, Addition of chemicals to cells Subsection); and

I) the effect of the substance on the or each biological target molecule is measured using a detection system coupled to the activation of the target molecule (Claims 94-103 and Page 57, line 5 to page 58, line 8); and/or

ii) the effect of the substance on different regulatory mechanisms triggered by the activation of the target molecule is determined by measuring the effects using a plurality of detection systems each coupled to the different regulatory mechanisms, and the effects of the test substance on the different test cells or the effects determined using different detection methods are directly compared with one another (Figure 20 and Page 58, line 13 to page 59, line 12).

Foulkes et al teach a process characterized in that a plurality of substances, optionally in several dilutions, are applied in parallel to one or more sets of cellular substrates, each set constituting a group of different assays or assay formats based on the same targeting cell (Claims 84-87 and page 56, Addition of chemicals to cells Subsection).

Foulkes et al teach a process characterized in that the test cells are mammalian and human cells (Claims 76-79 and Page 42, line 5 to page 43, line 11).

Foulkes et al teach a process characterized in that the test cells contain a reporter gene under the control of a regulatory sequence which responds to the change in the concentration of a messenger substance of a signal transmission pathway, of which the target molecule is a component, and that the effect of the test substance on the target molecule is determined in a change in the expression of the reporter gene (Figures 1-4, 6-9 and 11-12 and Page 57, line 5 to page 58, line 8 and Figures 20-24);

Foulkes et al teach a process characterized in that the reporter gene is luciferase (Figures 1-4, 6-9 and 11-12 and Page 57, line 5 to page 58, line 8).

Foulkes et al teach a process characterized in that the test cells which are dependent on a growth factor for their proliferation are cultivated in the presence of the growth factor and the effect of the substance on the cells is determined by indirectly measuring the apoptosis or the proliferation of the cells (Page 2, line 23 to page 5, line 5 and Page 42, line 5 to page 43, line 11 and Figure 20).

Foulkes et al teach a process wherein the cells are derived from a clone (Claim 91).

Foulkes et al teach a process wherein the target molecule is an intracellular component of a signal transmission pathway (Page 27, growth factor receptor).

Foulkes et al teach a process wherein the target molecule is tyrosine kinase (Page 6, lines 1-6).

Foulkes et al teach a process wherein the process is carried out in high throughput format with several dilutions of the substances (Page 60, line 10 to page 61, line 20).

Foulkes et al do not teach the method wherein the biological target molecules are receptor proteins.

Fodor et al teach the method wherein the biological target molecules are receptor proteins such as HER2 and Ras. (Column 5, lines 44-62).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the receptors HER2 and Ras of Fodor et al. in the process of Foulkes et al., since Fodor et al. state, "Such genes include, but are not limited to the HER2 proto-oncogene in the case of breast cancer, receptor tyrosine kinases (RTKs) associated with the etiology of a number of tumors including carcinomas in the breast, liver, bladder, pancreas, as well as glioblastomas, sarcomas, and squamous carcinomas, and tumor suppressor genes such as the p53 gene and other "marker" genes such as RAS, MSH2, MLH1 and BRCA1 (Column 5, lines 48-55)". An ordinary practitioner would have been motivated to combine and substitute the receptors HER2 and Ras of Fodor et al. in the process of Foulkes et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Fodor et al., of receptors which are used as "marker" associated with the etiology of a number of tumors including carcinomas in the breast, liver, bladder, pancreas, as well as glioblastomas, sarcomas, and squamous carcinomas, and tumor suppressor genes.

3. Claim 57 is rejected under 35 U.S.C. 103 (a) over Foulkes et al. (PCT international Publication number WO 92/13063) (August 6, 1992) in view of Fodor et al. (U.S. Patent

6,309,822 B1) (October 30, 2001) further in view of Chapman et al. (U.S. Patent 6,232,099 B1) (May 15, 2001).

Foulkes et al in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.

Foulkes et al in view of Fodor et al. do not teach the Green fluorescent protein as the reporter gene.

Chapman et al teach the Green fluorescent protein as the reporter gene (Examples 1 and 2 and Figures 1a and 1b).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al. in view of Fodor et al., since Chapman et al. state, "The green fluorescent protein (GFP) from A. Victoria is a reporter of gene expression in heterologous systems. GFP has an advantage over other marker proteins in that it can be detected non-invasively, without any requirement for exogenous substrates or co-factors since it fluoresces intrinsically without a requirement for exogenous substrate. In addition, fluorescence of GFP is retained in fusion proteins allowing the subcellular localization of fusion proteins (Column 7, line 66 to column 8, line 7)." An ordinary practitioner would have been motivated to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al. in view of Fodor et al. in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Chapman et

al., of a protein which has an advantage over other marker proteins in that it can be detected non-invasively, without any requirement for exogenous substrates or co-factors since it fluoresces intrinsically without a requirement for exogenous substrate and in addition, fluorescence of which is retained in fusion proteins allowing the subcellular localization of fusion proteins.

4. Claim 45 is rejected under 35 U.S.C. 103 (a) over Foulkes et al. (PCT international Publication number WO 92/13063) (August 6, 1992) in view of Fodor et al. (U.S. Patent 6,309,822 B1) (October 30, 2001) further in view of Bilodeau et al. (U.S. Patent 6,235,741 B1) (May 22, 2001).

Foulkes et al in view of Fodor et al. teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.

Foulkes et al in view of Fodor et al. do not teach the receptor KDR.

Bilodeau et al teach the receptor KDR. (Column 2, lines 1-16).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the receptors KDR of Bilodeau et al. in the process of Foulkes et al. in view of Fodor et al., since Bilodeau et al. state, "Inhibition of KDR or Flt-1 is implicated in pathological neoangiogenesis, and these are useful in the treatment of diseases in which neoangiogenesis is part of the overall pathology, e.g., diabetic retinal vascularization, as well as various forms of cancer (Column 2, lines 12-16))". An ordinary practitioner would have been motivated to combine and substitute the receptors KDR of Bilodeau et al. in the process of Foulkes et al. in view of Fodor et al., in order to improve the process for

determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Bilodeau et al., of KDR receptors which are implicated in pathological neoangiogenesis, and which are useful in the treatment of diseases in which neoangiogenesis is part of the overall pathology, e.g., diabetic retinal vascularization, as well as various forms of cancer.

5. Claim 47 is rejected under 35 U.S.C. 103 (a) over Foulkes et al. (PCT international Publication number WO 92/13063) (August 6, 1992) in view of Fodor et al. (U.S. Patent 6,309,822 B1) (October 30, 2001) further in view of Nishi et al. (U.S. Patent 6,159,967) (December 12, 2000).

Foulkes et al in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.

Foulkes et al in view of Fodor et al. do not teach the neurokinin receptor.

Nishi et al teach the neurokinin receptor. (Column 1, lines 30-40 and Column 244, line 65 to column 245, line 42).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the neurokinin receptor of Nishi et al. in the process of Foulkes et al. in view of Fodor et al., since Nishi et al. state, "The novel compounds of the present invention have a superior antagonistic effect on substance P and neurokinin receptors. Moreover since they have low toxicity, they are useful for the prevention and therapy of tachykinin-mediated diseases, examples of which include diseases of the central nervous system

including anxiety, depression, psychosis and schizophrenia (Column 244, line 65 to column 245, line 5)". An ordinary practitioner would have been motivated to combine and substitute the neurokinin receptor of Nishi et al. in the process of Foulkes et al. in view of Fodor et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Nishi et al., of neurokinin receptors which are implicated in diseases of the central nervous system including anxiety, depression, psychosis and schizophrenia.

6. Claim 48 is rejected under 35 U.S.C. 103 (a) over Foulkes et al. (PCT international Publication number WO 92/13063) (August 6, 1992) in view of Fodor et al. (U.S. Patent 6,309,822 B1) (October 30, 2001) further in view of Gerald et al. (U.S. Patent 6,331,401) (December 18, 2001).

Foulkes et al in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.

Foulkes et al in view of Fodor et al. do not teach the serotonin receptor.

Gerald et al teach the serotonin receptor. (Column 21, lines 16-50).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the serotonin receptor of Gerald et al. in the process of Foulkes et al. in view of Fodor et al., since Geraldet al. state, "Analysis of 5-HT4 structure and function provides a model for the development of drugs useful for the treatment of gastrointestinal conditions including bowel disease, postoperative ileus, diabetic gastroparesis,

emesis, achalesia, hiatal hernia, and esophagal spasm (Column 21, lines 22-27)". An ordinary practitioner would have been motivated to combine and substitute the serotonin receptor of Gerald et al. in the process of Foulkes et al. in view of Fodor et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Gerald et al., of serotonin receptors whose structure and function provides a model for the development of drugs useful for the treatment of gastrointestinal conditions including bowel disease, postoperative ileus, diabetic gastroparesis, emesis, achalesia, hiatal hernia, and esophagal spasm.

7. Claim 52 is rejected under 35 U.S.C. 103 (a) over Foulkes et al. (PCT international Publication number WO 92/13063) (August 6, 1992) in view of Fodor et al. (U.S. Patent 6,309,822 B1) (October 30, 2001) further in view of Johnson. (U.S. Patent 6,331,170 B1) (December 25, 2001).

Foulkes et al in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.

Foulkes et al in view of Fodor et al. do not teach the Raf receptor.

Johnson teaches the Raf receptor. (Column 5, lines 11-18).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Raf receptor of Johnson in the process of Foulkes et al. in view of Fodor et al., since Johnson states, "In particular, the method comprises regulating the apoptosis of the cell. Such a method is useful for the treatment of a medical

disorder. In particular, the method is useful for inhibiting tumorigenesis and autoimmunity (Column 5, lines 14-18)". An ordinary practitioner would have been motivated to combine and substitute the Raf receptor of Johnson in the process of Foulkes et al. in view of Fodor et al., since., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Johnson, of Raf receptors useful for the treatment of a medical disorder and in particular useful for inhibiting tumorigenesis and autoimmunity.

Response to Arguments

8. Applicant's arguments filed on April 17, 2003, with respect to withdrawal of 103(a) rejections of all pending claims, have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues on page 3, last paragraph to page 4, last paragraph that Foulkes et al does not teach the important element of the claimed invention, which is the detection of an agent that effects the activity of a biological target molecule that is a receptor protein. Applicant argues that Foulkes et al teaches only the detected agent that "binds to DNA or RNA, or binds to a protein at a site on such protein which is not a ligand-binding domain of a receptor which

naturally occurs in the cell". This argument is not persuasive. Foulkes et al clearly teaches the detection of an agent that up regulates and down regulates receptor protein, which indirectly and inherently affects the activity of a biological target molecule that is a receptor protein (Page 34, line 30 to page 37, line 12). Moreover, it is not a requirement of the pending claims that the detecting agent and the receptor proteins have to interact directly for the manifestation of the effects of the detecting agent on the activity of the biological target molecule.

Applicant then argues (page 6, first paragraph, page 8, second paragraph, page 10, last paragraph, page 13, firs paragraph, page 14, last paragraph to page 15, third paragraph, page 17, second paragraph, page 20, second paragraph, lines 3-4) that the 103 rejections are improper because all combinatory references are "obvious to try" and lack a reasonable expectation of success.

With regard to the "obvious to try" argument, The MPEP 2143.02 states "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up

in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Gerald reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different chemical compounds were actually experimentally studied and found to be functional by specifically binding to a rat or human serotonin receptors (Tables 1-6 and Abstract). This evidence of functionality trumps the attorney arguments, which argues that Gerald reference is an invitation to research, since Gerald steps beyond research and shows the functional product. This logic is applicable to other combinatory references as well.

Applicant also argues (page 8, second paragraph and page 10, second paragraph) that there are no motivations to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Fodor et al. since Fodor et al. state, "Such genes

include, but are not limited to the HER2 proto-oncogene in the case of breast cancer, receptor tyrosine kinases (RTKs) associated with the etiology of a number of tumors including carcinomas in the breast, liver, bladder, pancreas, as well as glioblastomas, sarcomas, and squamous carcinomas, and tumor suppressor genes such as the p53 gene and other "marker" genes such as RAS, MSH2, MLH1 and BRCA1 (Column 5, lines 48-55)". This logic is applicable to other combinatory references as well.

Applicant also argues (page 5, last paragraph) that Fodor et al reference does not teach the receptors and only teaches the genes encoding the receptors. This argument is not persuasive. Fodor et al clearly teaches the proteins and antibodies which interact with each other (Column 56, lines 9-60, Non-polynucleotide embodiments).

Applicant also argues (Page 12, second paragraph) that Nishi et al has a motivation, which is different from the applicant. This argument is not persuasive. In response to applicant's argument, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant also argues (Page 16, last paragraph) that Johnson reference does not teach the Raf receptor. This argument is not persuasive. Johnson clearly teaches the Raf receptor (Figure 2).

In view of ths response to argument, all 103(a) rejections except the rejection of claim 54 based on O'Hare reference, made in the previous office action are hereby properly maintained.

Allowable Subject Matter

9. Applicant's argument to withdraw the rejection of claim 54 is persuasive. Therefore, in absence of a teaching and motivation to use bcl-2 receptor, claim 54 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 746-4979.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

May 7, 2003

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